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Postoperative Immunostimulation after Complete Resection Improves Survival of Patients with Stage I Nonsmall Cell Lung Carcinoma

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BACKGROUND. Approximately 40% of primary lung carcinoma patients who die within 1 month after a complete resection have residual tumor in regional or distant organs, emphasizing the importance of postoperative adjuvant therapy. In this study, the effectiveness of transfer factor (TF) and nocardia rubra-cell wall skeleton (N-CWS) as adjuvant therapy for patients with primary, completely resected nonsmall cell carcinoma of the lung was evaluated in a randomized controlled trial.

METHODS. A total of 82 patients with Stage I disease who had a complete resection were allocated randomly into 2 groups: TF + N-CWS (n = 41) or control (surgery only) (n = 41).

RESULTS. The distributions of age, sex, histology, differentiation, T classification, tumor size, visceral pleural invasion, and the site of origin, were similar in the two groups. The 5- and 10-year disease specific survival rates in the TF + N-CSW group were 85% and 85%, respectively, and those in the control group were 72% and 64%, respectively. There was a statistically significant difference between the two groups ($P = 0.041$). When the survival was analyzed according to clinical characteristics, significant differences were observed in patients with no visceral pleural invasion or with T1 disease. The frequency of distant metastasis was significantly less in the TF + N-CWS group than in the control group.

CONCLUSIONS. These results indicate that TF + N-CWS is beneficial as adjuvant therapy after surgical treatment of Stage I nonsmall cell carcinoma of the lung. *Cancer* **1996; 78:1892–8.** © *1996 American Cancer Society.*

KEYWORDS: transfer factor, nocardia rubra-cell wall skeleton, lung carcinoma, immunotherapy, surgery, adjuvant therapy.

In patients with nonsmall cell lung carcinoma, it is known that there is a high incidence of micrometastasis in distant organs at the time of resection, even though the resection is complete.[1–3] This emphasizes the importance of postoperative adjuvant therapy to suppress the growth of micrometastasis. Transfer factor (TF) is a low molecular weight, nonimmunogenic and dialyzable material of disrupted human peripheral leukocytes that transfers cell-mediated immunity including delayed cutaneous hypersensitivity reactions to nonimmune recipients.[4,5] Lung carcinoma patients were treated with TF in a randomized controlled trial using chemotherapy as the standard therapy. TF was found to be effective in Stages I and II, as an adjuvant to surgical resection.[6]

The nocardia rubra-cell wall skeleton (N-CWS) is a CWS fraction from nocardia rubra comprised of nocardomycolic acid, arabinogalactan, and mucopeptide, which induces killer T-cells, and has been

shown to be effective in the suppression of transplantable tumors in syngeneic mice.[7] Clinical trials of adjuvant immunotherapy with N-CWS in patients with lung carcinoma showed significant efficacy on survival rates only in curatively resected patients.[8] This trial was also performed using chemotherapy as the standard therapy. However, it is difficult to interpret the mechanisms of immunopotentiators when combined with chemotherapy, and recent authors have reported no clinical benefit of adjuvant chemotherapy in Stage I lung carcinoma patients.[9]

Based on these reports, adoptive and active immunotherapeutic agents, TF and N-CWS, were combined that might be more potent than a single agent in improving the results of lung carcinoma patients with complete resection, without the administration of chemotherapeutic drugs. In this study, the effects of adjuvant TF and N-CWS administration after surgical treatment in patients with Stage I nonsmall cell lung carcinoma in a randomized controlled trial of TF + N-CWS versus surgery alone with 6 to 10 years of follow-up are described.

MATERIALS AND METHODS

Patients

Between 1986 and 1990, 82 patients with nonsmall cell lung carcinoma who had undergone a complete resection and mediastinal lymph node dissection were entered in this study. They were randomized into two groups, TF + N-CWS or control, by closed envelope 2 weeks after their surgery, when the pathologic examination of the resected materials documented Stage I carcinoma. No stratification criteria were used in the randomization. The control group patients received surgery alone without any particular treatment until recurrence. All patients underwent lobectomy with mediastinal lymph node dissection, except for one patient in the control group who underwent pneumonectomy. The eligibility criteria was as follows: 1) nonsmall cell carcinoma; 2) pathologic Stage T1N0M0 or T2N0M0 disease; 3) complete resection; 4) age younger than 75 years; 5) Karnofsky performance status of 90% or greater; 6) no other active malignancy; 7) no hepatorenal dysfunction; and 8) no severe complications. The patients were seen every 2 weeks during the first postoperative year, every 3 months during the 2nd to 5th postoperative years, and every 6 months thereafter. Additional follow-up and survival date were acquired by phone or postcard contact with each patient. Informed consent was obtained from each patient. One patient was lost to follow-up at 72 months. The follow-up was complete for the remaining patients through December, 1995.

Histologic Examination

Histology and stage were classified according to the criteria reported by Mountain[10] and the general rule for clinical and pathologic recording for lung carcinoma, edited by the Japan Lung Cancer Society.[11] Cellular differentiation was graded as well, moderately, and poorly differentiated for those patients with nonlarge cell histology. Large cell carcinomas were labeled as undifferentiated.[12] Primary tumors originating at a segmental or lobar bronchus, and those at a subsegmental bronchus or peripheral region were classified as being of hilar or peripheral origin, respectively.

TF and N-CWS Administration

TF was prepared by a modification of the method of Lawrence and Al-Askari.[13] Approximately 5×10^9 to 1×10^{10} peripheral lymphocytes were harvested from family members who had good immune status of each patient by leukopheresis with a discontinuous blood cell separator (Haemonetics Model 30; Haemonetics Co., Boston, MA). Informed consent was obtained from each donor prior to the procedure, and the donors were negative for human immunodeficiency virus and hepatitis B antigens. Pooled peripheral lymphocytes were resuspended in pyrogen-free saline at a concentration of 2.5×10^8 cells/mL. The suspension was frozen and thawed 7 times, then centrifuged at 10,000 g for 30 minutes. Prewashed dialysis tubing with a molecular weight cutoff of 12,000 was inserted into a ProDifilt negative-pressure dialysis apparatus (Biomolecular Dynamics, Beaverton, OR). The cell lysate was then added to the tubing. The dialysate was filtered through a 0.2-μm filter, cultured for bacteria, assayed for endotoxin and hepatitis B antigen, and stored frozen at −80 °C until use. N-CWS was kindly provided by the Fujisawa Pharmaceutical Co. (Osaka, Japan). One vial of TF, equivalent to 5×10^8 peripheral lymphocytes, was administered subcutaneously (sc) every 4 weeks, and N-CWS (200 mg) was administered sc every 2 weeks beginning 1 month after resections, and continuing for 1 year.

Statistical Analysis

Differences in the TF + N-CWS and control groups with respect to age, sex, histology, differentiation, T classification, tumor size, visceral pleural invasion (VPI), and the site of origin were analyzed by the chi-square test. Differences in the distribution of metastases between the two groups also were evaluated by the chi-square test. Survival times and times to first recurrence were measured from the day of surgery. Actuarial overall survival, disease specific survival, and recurrence free survival curves were calculated by the Kaplan–Meier method[14] and analyzed by the log rank

TABLE 1
Clinical Characteristics of the Patients

Characteristic	TF + N-CWS (n = 41)	Control (n = 41)	Chi-square (*P* value)
Age (yrs)			
< 60	21	15	
60–69	11	17	
≥ 70	9	9	0.319
Sex			
Male	29	28	
Female	12	13	0.81
Histology			
Adenoca	24	24	
Squamous cell ca	13	16	
Large cell ca	4	1	0.348
Differentiation			
Well	8	5	
Moderate	21	29	
Poor	8	6	
Undifferentiated	4	1	0.255
T classification			
T1	25	23	
T2	16	18	0.654
Tumor size (mm)			
30 or less	25	25	
31–49	11	12	
50 or more	5	4	0.926
VPI			
Absent	32	34	
Present	9	7	0.577
Origin			
Periphery	5	6	
Hilum	36	35	0.746

TF: transfer factor; N-CWS: nocardia rubra-cell wall skeleton; Adenoca: adenocarcinoma; ca: carcinoma; VPI, visceral pleural invasion.

test.[15] The disease specific survival also was analyzed by the Cox proportional hazards model with covariates,[16] using the statistical software program package SPSS (SPSS Version 6.1 for Windows; SPSS Inc., Chicago, IL). *P* values < 0.05 were considered statistically significant.

RESULTS

Patients

There were no statistically significant differences between the two groups with respect to age, sex, histology, cellular differentiation, T classification, tumor size, VPI, or site of origin of the primary tumor (Table 1). The follow-up interval ranged from 7 to 116 months with an average of 99 months in the TF + N-CWS group and from 3 to 118 months with an average of 83 months in the control group. During the follow-up period, two other malignancies (one gastric carcinoma and one second primary squamous cell carcinoma of the carina) developed in the TF + N-CWS group. Three other malignancies (one colon carcinoma, one tongue carcinoma, and one second primary adenocarcinoma of the lung) developed in the control group. All five patients were treated with curative intent by surgery or endoscopic treatment. Four patients were alive without recurrence at the time of last follow-up. The patient with gastric carcinoma died from liver metastasis. Thirty-three and 24 patients were alive in the TF + N-CWS and control groups, respectively. Their follow-up intervals ranged from 61 to 116 months with an average of 81 months in the TF + N-CWS group, and from 66 to 118 months with an average of 74 months in the control group. Thirty-five of the 41 patients in the TF + N-CWS group had slight sc induration at the site of the N-CWS injection that did not prevent further administration of TF and N-CWS. However, one patient had severe induration with local erythema at 6 months postoperatively, and only TF was administered thereafter. Slight fever (37.2–37.5 °C) occurred in 1 patient with severe induration in TF + N-CWS group. The transient elevation of glutamic oxaloacetic transaminase and glutamic pyruvic transaminase values (40–60 mU/dL) occurred in 4 and 3 patients, respectively, in the TF + N-CWS and control groups. No other particular complications were experienced.

Overall Survival and Disease Specific Survival

Overall survival at both 5 and 10 years was 80% for both in the TF + N-CWS group and 65% and 59%, respectively, in the control group and there was no statistically significant difference between the 2 groups. Disease specific survival at 5 and 10 years was 85% for both in the TF + N-CWS group, and 72% and 64%, respectively, in the control group (Fig. 1.) There was a statistically significant difference between the two groups ($P = 0.041$). When the covariates of age, sex, histology, differentiation, T classification, VPI, and the site of origin were included, a statistically significant difference was demonstrated between the TF + N-CWS and control groups ($P = 0.017$, relative risk 2.018, 95% confidence interval, 1.132–3.597).

Disease Specific Survival According to Clinical Characteristics

The 5- and 10-year disease specific survival rates of patients with T1 tumors in the TF + N-CWS group were both 92%, and those of patients with T1 tumors in the control group were 77% and 68%, respectively (Fig. 2). There was a statistically significant difference between the two groups ($P = 0.048$). Among the patients with T2 disease, the survival rates at 5 and 10 years were both 74% in the TF + N-CWS group, and

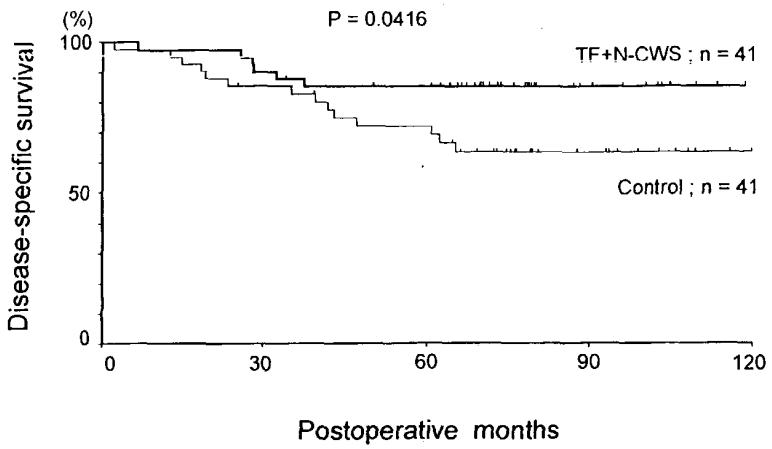

FIGURE 1. Disease specific survival curves of the two groups.

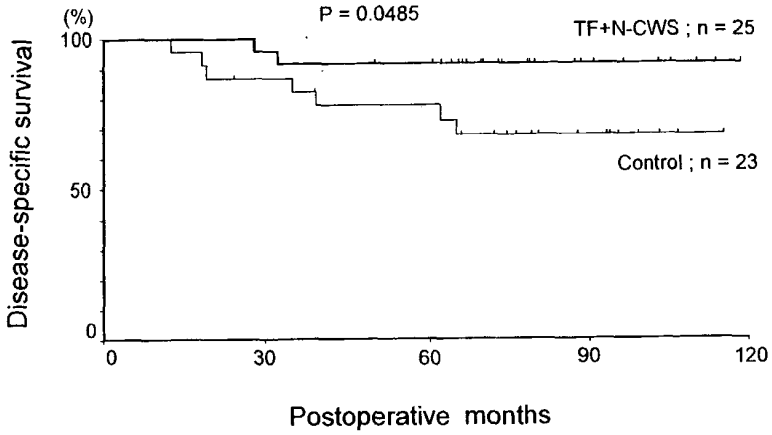

FIGURE 2. Disease specific survival curves in patients with T1 disease.

64% and 58%, respectively, in the control group. No statistically significant difference was demonstrated.

The 5- and 10-year survival rates of the TF + N-CWS group without VPI were both 90%. Those of the control group without VPI were 76% and 66%, respectively (Fig. 3). A statistically significant difference was demonstrated between the two groups ($P = 0.023$). However, the survival rates at 5 and 10 years were both 65% in the TF + N-CWS group with VPI. Those in the control group with VPI were both 51%. No significant difference was demonstrated between the two groups.

There were no significant differences between the TF + N-CWS group and the control group when survival was evaluated by the distribution of other clinical characteristics, including age, sex, histology, differentiation, and the site of origin.

Recurrence Free Survival, Metastatic Pattern, and Cause of Death

The recurrence free survival at 5 and 10 years was 85% and 78%, respectively, in the TF + N-CWS group, and both 65% in the control group (Fig. 4). No statistically significant difference was demonstrated between the two groups.

Regarding the pattern of metastases (Table 2), a total of 7 patients (17%) recurred in the TF + N-CWS group, and 14 patients (34%) recurred in the control group. Local recurrence was demonstrated in three patients in each group. However, the frequency of distant metastasis was significantly lower in the TF + N-CWS group than in the control group ($P = 0.042$). The cause of death of the majority of patients was metastasis. During the follow-up period, one patient in the control group died from a heart attack and 1 from stroke, without any recurrence in postoperative Months 25 and 39. One patient in the TF + N-CWS group died from pneumonia and 1 from gastric carcinomas in postoperative Months 34 and 51.

DISCUSSION

Surgical treatment is the only curative modality for patients with nonsmall cell lung carcinoma. However, post-

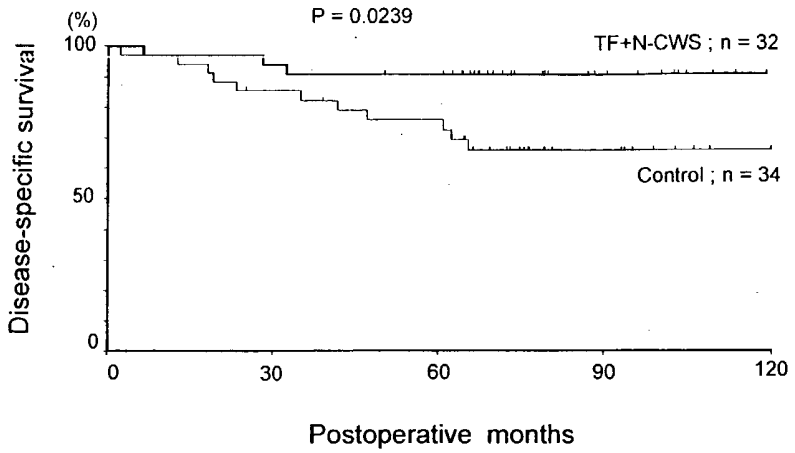

FIGURE 3. Disease specific survival curves in patients without visceral pleural invasion.

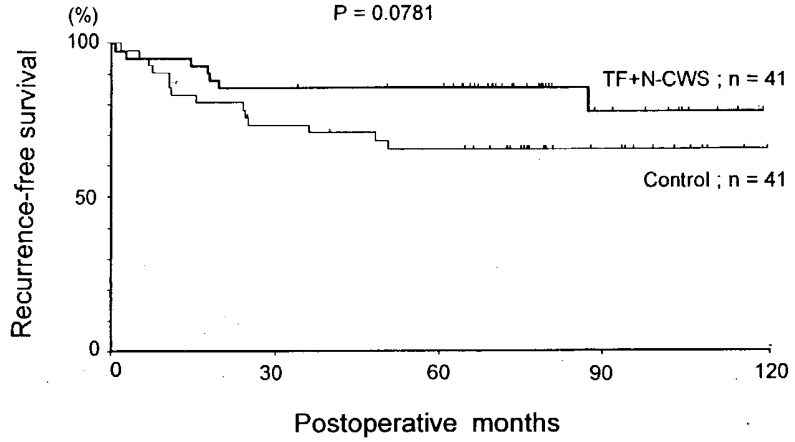

FIGURE 4. Recurrence free survival curves of the two groups.

operative recurrence occurred in approximately 40% of the resected patients with Stage I disease.[17] Therefore, effective postoperative adjuvant therapy will be necessary to improve the results of surgical treatment in patients with Stage I lung carcinoma. Postsurgical adjuvant chemotherapy with cyclophosphamide, doxorubicin, and cisplatin (CAP) has been evaluated in patients with advanced disease and the study was not randomized.[18] Recently, two randomized, controlled studies were performed using adjuvant chemotherapy with CAP in patients with completely resected Stage I nonsmall cell lung carcinoma, with controversial results.[9,19] The significance of CAP chemotherapy as an adjunct treatment to surgery has not been established.

Randomized controlled trials of immunotherapy with TF or N-CWS as an adjunct to surgical treatment for patients with nonsmall cell lung carcinoma have been reported by the authors[6] and by Yasumoto et al.[8] Both showed a significant improvement in survival in resected patients, especially those with a complete resection. However, chemotherapeutic agents, including mitomycin-C, 5-fluorouracil, cyclophosphamide, methotrexate, chromomycin-A3, and vincristine were administered as the standard therapy, which might result in substantial immunosuppression, making it difficult to interpret the results of the studies. In this study, the effectiveness of TF and N-CWS as adjuvant treatment in patients with completely resected, Stage I nonsmall cell lung carcinoma was evaluated in a randomized, controlled trial that included a surgery-alone control group. The overall result demonstrated a significant prolonged disease specific survival and a trend toward prolonged recurrence free survival by the suppression of distant metastasis in the treatment group, and a significant effectiveness of TF and N-CWS on survival in patients with T1 disease or no VPI.

TABLE 2
Metastatic Patterns and Cause of Death in the TF + N-CWS and Control Groups

	TF + N-CWS (n = 41)	Control (n = 41)	Significance[a]
Metastatic pattern			
Local recurrence	3[b]	3	
Distant metastasis	4	11	$P = 0.0421$
Lung	2	6	
Brain	2	1	
Multiple organs	0	4	
Cause of death			
Metastasis	6	14	$P = 0.0397$
Another malignancy	1	0	
Nonmalignant cause	1	2	

TF: transfer factor; N-CWS: nocardia rubra-cell wall skeleton.
[a] Chi-square test.
[b] No. of patients.

The results of immunotherapy for Stage I nonsmall cell lung carcinoma in other randomized clinical trials have been controversial. Mountain and Gail[20] have reported no effect of intrapleural bacille Calmette-Guérin (BCG). However, the follow-up interval was relatively short. Little et al.[21] have demonstrated that immunotherapy with BCG skin scarification holds sufficient promise to warrant further investigation, and that the effectiveness of immunotherapy should be analyzed after long term follow-up. The differences between the results of Mountain and Gail[20] and Little et al.[21] might depend on differences in the route of administration and the follow-up interval. In addition, the systemic and local intensity of the antitumor effector mechanism induced by BCG may be different in the two studies. A randomized trial of intrapleural *Corynebacterium parvum* (*C. parvum*) as postoperative adjuvant therapy for patients with Stage I or II nonsmall cell lung carcinoma showed a significant decrease in survival in the *C. parvum* group.[22]

Whyte et al.[23] have reported the possible effectiveness of TF on 10-year survival in patients with Stages I, II, and III disease. In this study, a significant effect of TF and N-CWS on the prolongation of survival and the disease free interval was found in Stage I patients when the results were evaluated statistically with the Cox proportional hazards model with covariates. This clinical effectiveness appears to be correlated with the multiplication effect of TF and N-CWS. The authors previously reported the strong activity of TF on the restoration and augmentation of weak or latent delayed type cutaneous hypersensitivity reactions.[24] One of the possible immune mechanisms generated in vivo in the current study includes TF augmentation of the antitumor immune function induced by N-CWS.[7]

Several investigators on prognostic factors in patients with resected Stage I nonsmall cell lung carcinoma have elucidated that vascular invasion, VPI, and tumor size more than 3 cm in maximum diameter are independent factors by multivariate analysis,[25] and predict a higher recurrence rate in nonsquamous cell carcinoma.[26] These reports indicate that patients with Stage I nonsmall cell lung carcinoma can be stratified into high and low risk populations that can be used in future randomized trials of adjuvant therapy. The relationship between prognostic factors and the indications for immunotherapy remains obscure.

In this study, a significant effectiveness of postoperative immunostimulation with TF and N-CWS in a T1 subset of nonsmall cell lung carcinoma patients was found. The survival in the control group was very similar to that previously reported,[21,25,26] so it is obvious that this finding was not due to a control group that happened to have unusually poor survival. Patients with T1N0M0 nonsmall cell lung carcinoma are thought to be candidates for immunostimulation as adjuvant therapy after complete resection.

In conclusion, although the effects of immunotherapy are unproven, there is evidence that the enhancement of immune status may improve survival in patients with completely resected nonsmall cell lung carcinoma.[27] In the current study of patients followed for 6 to 10 years, survival and recurrence free survival were consistently better in the immunotherapy group than in the surgery-alone control group. These data suggest the importance of the augmentation of immunity in patients with resected, Stage I nonsmall cell lung carcinoma. These immunotherapeutic approaches should be investigated further.

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Postoperative immunostimulation after complete resection improves survival of patients with stage I nonsmall cell lung carcinoma.

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BACKGROUND: approximately 40% of primary lung carcinoma patients who die within 1 month after a complete resection have residual tumor in regional or distant organs, emphasizing the importance of postoperative adjuvant therapy. In this study, the effectiveness of transfer factor (TF) and nocardia rubra-cell wall skeleton (N-CWS) as adjuvant therapy for patients with primary, completely resected nonsmall cell carcinoma of the lung was evaluated in a randomized controlled trial METHODS: A total of 82 patients with Stage I disease who had a complete resection were allocated randomly into 2 groups: TF + N-CWS (n = 41) or control (surgery only) (n = 41). RESULTS: The distributions of age, sex, histology, differentiation, T classification, tumor size, visceral pleural invasion, and the site of origin, were similar in the two groups. The 5- and 10-year disease specific survival rates in the TF + N-CWS group were 85% and 85%, respectively, and those in the control group were 72% and 64%, respectively. There was a statistically significant difference between the two groups (P = 0.041). When the survival was analyzed according to clinical characteristics, significant differences were observed in patients with no visceral pleural invasion or with T1 disease. The frequency of distant metastasis was significantly less in the TF + N-CWS group than in the control group. CONCLUSIONS: These results indicate that TF + N-CWS is beneficial as adjuvant therapy after surgical treatment of Stage I nonsmall cell carcinoma of the lung.

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- Clinical Trial
- Randomized Controlled Trial

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